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Keratoacanthoma

Experimentally Induced with Methylcholanthrene in the Chicken

R. H. RIGDON, M.D., Galveston, Texas

In 1934, Ferguson Smith[1] described a self-healing squamous-cell epithelioma in the skin of a man 23 years of age. In 1955, Ereaux and associates[2] reported a case in which there were widespread self-healing epithelial tumors in the skin of a white man 41 years of age that were considered keratoacanthomas. The clinical and histologic characteristics of this lesion have been described.[2-18] A new classification of keratoacanthomas in three histological types, Types 1, 2, and 3, has been suggested recently by Ghadially.[19]

In considering the etiology of the localized type of keratoacanthoma, Anderson,[2] in the discussion of Ereaux's paper, says, "One is impressed . . . as to the frequent history of preceding trauma, such as a cut, scratch, or the squeezing of a blackhead. There is no doubt that very similar, if not identical, lesions occur in those exposed to tar." Actinic or oil sensitization has been implicated,[16] also sunlight[18] and oil and tar.[4] There are observations that would suggest a viral origin.[2] Since some of the cases have been observed in members of a family, there may be a genetic factor.[3,17]

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Professor of Pathology, The University of Texas—Medical Branch.

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In the study of carcinogenesis in the chicken,[20-22] we have observed lesions in the skin following local applications of methylcholanthrene characterized by a macule that subsequently progressed in size and ulcerated. Histologically, the lesion has all the characteristics of a squamous-cell carcinoma, but it spontaneously regresses. This lesion in the chicken is described at this time because of its similarity to keratoacanthoma.

Methods and Material

The technique used to produce these tumors has been reported.[20] A 0.25% solution of methylocholanthrene in acetone was applied to the skin of the body beneath the wing and to the undersurface of the wing. The acetone solution of methylcholanthrene, 0.2 ml., was used on the day-old chicks, and 1 ml. was used on the older birds. The applications of the carcinogen were made daily, except for Saturdays and Sundays. The total number of applications for any one bird varied from 1 to 30. In some experiments the feathers were plucked, either before, during, or after the methylcholanthrene was applied. The lesions sometimes were either biopsied or completely excised for histologic study.

Results

The details of the experimental observations made in this study have been reported.[20,21] The earliest tumor occurred 23 days after the first application of methylcholanthrene. The longest interval between the first application of methylcholanthrene and the development of a tumor was 128 days. Eight was the largest number of

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Fig. 1.—The center of these squamous-cell tumors is filled with keratin. Hematoxylin and eosin; reduced 20% from mag. × 19.

tumors observed at one time in any one chicken. The lesions, when first observed, were nodules about 2 mm. in diameter. They progressively grew, and their centers were filled with keratin (Fig. 1). They subsequently ulcerated (Figs. 2, 3, and 4). The size of the ulcers varied from 3 to 12 mm. The base was granular; the periphery was hyperplastic, and the edges were undetermined. Healing seemed to progress rapidly from both the base and the periphery; a typical scar resulted.

Histologically, the lesion always was characterized by squamous cells (Fig. 5). Intercellular bridges (Fig. 6) were conspicuous in some, while in others typical epithelial pearls were present. Keratin and mitotic cells were numerous in some of the lesions (Figs. 7 and 8). Polymorphonuclear leukocytes were present in the crater of the tumors. Leukocytes, mononuclear cells, and groups of lymphocytes were present in the surrounding dermis (Figs. 9 and 10). Polymorphonuclear leukocytes frequently were prominent about the periphery of the tumor. Extensive degeneration occurred in the squamous cells at the periphery of the growth (Fig. 11). The degree of degeneration varied in the different lesions, both within the same chickens and in different birds. Ultimately, the squamous cells in the tumor completely degenerated; the leukocytes phagocytized the debris, and collagen fibers filled the area.

This degenerative change in the tumor is most pronounced and seems to begin at the periphery of the growth. It proceeds inward until all the epithelial cells are destroyed. The time for regression varied from two weeks to two months.

Comment

The tumors that develop in the skin of chickens following the local application of methylcholanthrene resemble in many ways the keratoacanthoma described in man by McNulty and Sommers.[16] They have described this lesion as follows:

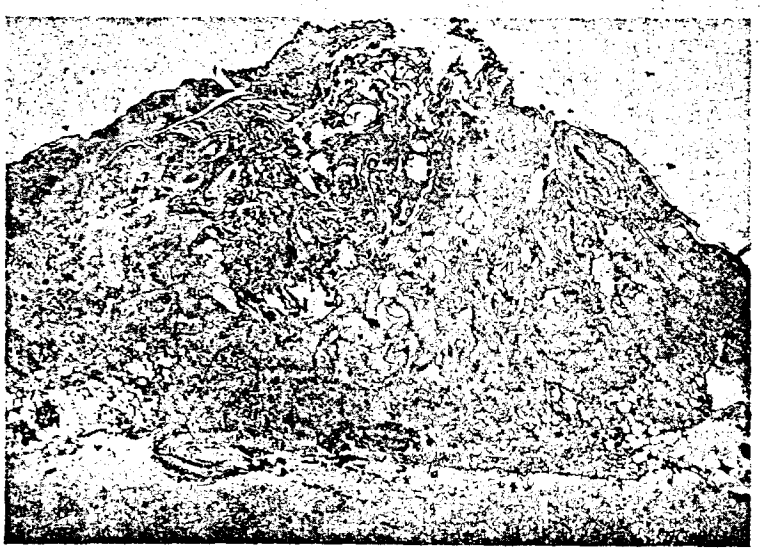

Fig. 2.—This chicken was 77 days of age when 1.0 ml. of the solution of methylcholanthrene was applied daily for 30 days except for Saturdays and Sundays. The lesion was first observed on the 75th day after the first application of methylcholanthrene. Photographed on the 99th day.

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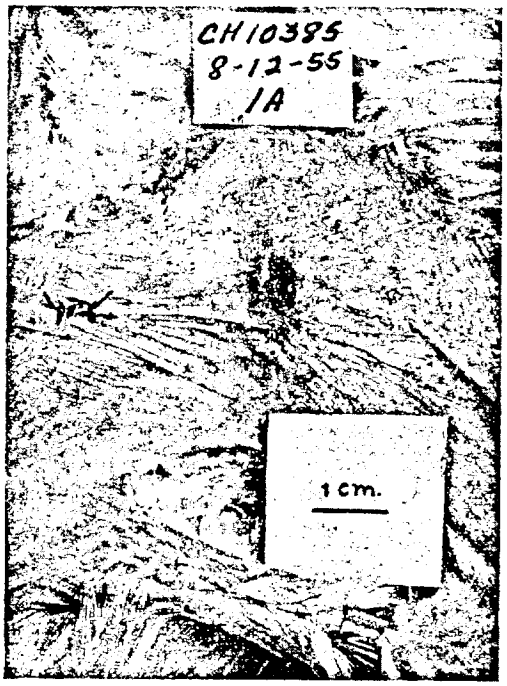

Fig. 3.—Treated same as chicken shown in Figure 1. Photographed on the 105th day after the first application of methylcholanthrene.

Fig. 4.—Treated same as chicken shown in Figure 1. Photographed on the 47th day after the first application of methylcholanthrene. The tumor was 1.0 cm. at this time.

. . . crateriform, with masses of keratin packed in centrally and superficially . . . On section the mass is pulpy, moist, keratinaceous, exudes a cloudy fluid, and has a crumbling yellow-brown appearance . . . rounded masses of partly keratinized cells with abundant ground-glass-like eosinophilic cytoplasm and prominent intercellular bridges are bulging downward into the dermis and everting the marginal unaffected epithelium . . . . The basement membrane boundary zones are obscured or lost, and a heavy infiltrate of leucocytes surrounds and overflows into the epithelial downgrowths . . . . Under higher magnification the diffuse mingling of leucocytes, particularly neutrophils, eosinophils, and lymphocytes, with sheets of epithelium is further emphasized . . . . Plasma cells, lymphocytes

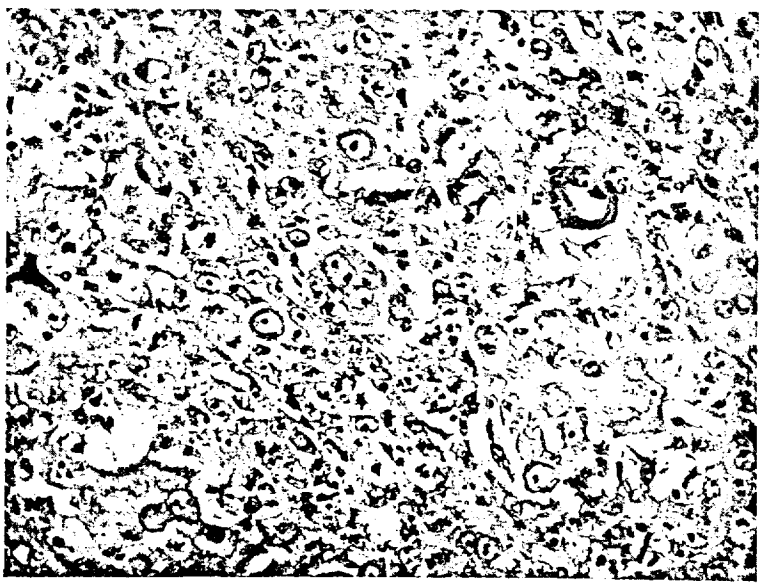

Fig. 5.—The squamous epithelial cells vary in size and shape. Epithelial pearls do occur. Mitotic figures are present. Hematoxylin and eosin; reduced 10% from mag. × 340.

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Fig. 6.—Intercellular bridges are present in some of these squamous-cell tumors in the chicken. Hematoxylin and eosin; × 800.

Fig. 7.—These are groups of squamous cells with ground-glass-like eosinophilic cytoplasm in focal areas of these tumors. Observe the large number of polymorphonuclear leukocytes. Hematoxylin and eosin; × 340.

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Fig. 8.—Atypical mitotic cells are present in these tumors. Hematoxylin and eosin; × 800.

Fig. 9.—The periphery of these tumors is usually infiltrated with lymphocytes and leukocytes. Hematoxylin and eosin; × 170.

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Fig. 10.—Many lymphocytes usually are present about the periphery of these lesions. Hematoxylin and eosin; × 340.

Fig. 11.—The nuclei of the squamous cells at the periphery of these regressing lesions are pyknotic. Subsequently, these cells atrophy and ultimately completely disappear. Hematoxylin and eosin; × 340.

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and macrophages are around the epithelium in abundance. Degenerative cytologic epithelial changes are uniformly present and distinctive . . . . Mitoses are abundant in the hyperplastic epithelium and abnormal mitotic figures with chromosomal fragmentation and dispersion, usually outnumber the normal mitoses . . . . In the adjacent dermis, detached epithelial cells heavily infiltrated with leucocytes are found in keratoacanthoma.

The similarity of this lesion induced with methylcholanthrene in the skin of the chicken and the description of keratoacanthoma, as given by McNulty and Sommers,[16] is obvious. It is my opinion, and the opinion of others who have studied this lesion in the skin of chickens, that it is histologically a low-grade malignant epithelial tumor. However, since it regresses and does not metastasize, it has been described as a "squamous-cell carcinomatoid tumor," [21] although originally we reported it as a "squamous-cell carcinoma." [20] The problems in the differentiation of keratoacanthoma, squamous-cell carcinoma, and pseudoepitheliomatous hyperplasia are readily appreciated and have been discussed frequently.

The most interesting features about keratoacanthoma in man and the carcinomatoid tumors in chickens induced by methylcholanthrene are their histologic resemblance to squamous-cell carcinomas and their spontaneous regression. An increasing number of malignant tumors that regress spontaneously is being found in man and animals.[23-27] Little is known, however, as to the mechanism of regression. Haaland [28] suggested that a change must occur within the tumor cell to explain this phenomenon. Huggins [29] has emphasized the role of hormones in the regression of certain neoplasms. Cowdry,[30] in discussing the problems of "unexplained disappearance and alterations in the malignancy of cancer cells," suggests that "spontaneous modifications in the volume, or growth, of a cancer could result from many variables both of the malignant cells and of the stroma." Experimentally induced hemangiomas spontaneously regress as a result of a mechanical obstruction that occurs within the vascular channels. With the progressive decrease in blood flow through the vascular channels, tissue anoxia may become the significant factor in the mechanism of this spontaneous regression.[31]

The observation that the degree of cellular degeneration is more marked in the cells at the periphery of the chicken tumor induced by methylcholanthrene would suggest that some cellular injurious factor reaches these cells by way of the tissue fluid. Antibodies formed elsewhere in the body, reacting with the antigen represented by the proliferated epithelial cells, could account for this degeneration of the tumor cells. The degeneration might be expected to begin at the periphery of the lesion. In support of this hypothesis are the observations of Pollard and Bussell,[32,33] who found an inhibition of growth of methylcholanthrene-induced tumor tissue when the transplants were grown in the presence of splenic tissue obtained from mice previously inoculated subcutaneously with methylcholanthrene. This tumor-destructive effect could not be demonstrated with "normal" spleens or with the spleens from mice supplying the tumor tissue. Furthermore, this reaction could not be induced with spleens from mice treated with other carcinogens; too, when a carcinogenically induced transmissible tumor involuted, the recovered host was refractory to reinoculation with the same tumor.

It would seem of interest to observe persons with keratoacanthomas closely from an immunological standpoint. A regression of these lesions may be related in some way to an immune process. In view of the histological similarity of the keratoacanthoma and a low-grade squamous-cell carcinoma, it might be that some immune process occurs in the person to account for the regression of the former lesion. A history referable to the resistance to bacterial infections, allergic manifestations, and serologic and chemical observations on the serum might contribute something to the mechanism of regression of neoplasms, a process that rarely occurs in man but does occur frequently in laboratory animals.

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Ghadially,[19] in 1958, pointed out the similarity of lesions produced by 9:10-dimethyl-1:2-benzanthracene in the skin of the rabbit to keratoacanthomas in man. The paper by Ghadially[19] came to my attention after this manuscript had been prepared. It is of considerable interest, however, to observe the close similarity of the history and the morphology of these lesions in man and the rabbit. Too, the lesions in the chicken are very similar to those in the rabbit. Keratoacanthomas, according to Ghadially,[19] appear to start by hyperplasia of the hair follicles and metaplasia of the sebaceous glands. Fragments of hair shafts often persist; this lends support to the suggestion that these lesions arise from hair follicles and not as downgrowths from the epidermis.[19] The fact that multiple lesions histologically similar to keratoacanthomas can be produced in the rabbit with carcinogens suggests the possibility that cases of multiple self-healing carcinomas may be no more than multiple keratoacanthomas arising in a genetically susceptible group of persons exposed perhaps to an undetected carcinogenic stimulus.[19]

Summary

A squamous-cell tumor occurs in the skin of chickens after the local application of methylcholanthrene. This tumor is characterized by a crater in which there is a large amount of keratin and leukocytes. Lymphocytes, histocytes, and leukocytes are present at the periphery of the growth. The tumor spontaneously regresses. The similarity of this squamous-cell tumor in the chicken to the keratoacanthoma in man is discussed.

University of Texas Medical Branch.

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